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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/637,302	HOOD ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed May 21, 2004 amending claims 1, 3, 14 and 15 and canceling claim 41 has been entered.

Claims 1, 3, 5, 6, 14 and 15 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5, 6, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, with dependent claims 3, 5, 6, 14 and 15, recites "at least about 0.1 weight percent of a Raf protein" rendering the metes and bounds of the claim indefinite (emphasis added). The term "at least" means "no less than 0.1 percent" whereas "at least about" encompasses values below 0.1 as well. Furthermore, there is no antecedent basis for the term "the active Raf protein" on line 8 (emphasis added).

Claim Rejections - 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

> subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5, 6, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freed et al. alone or in view of Przybyszewska et al.

Freed et al. (US Patent 5,597,719, form PTO-892 mailed July 15, 2003) teach human Raf protein of SEQ ID NO:2 that is 100% identical to SEQ ID NO:2 of the instant invention and its functional fragments (columns 1-4, line 15). Said fragments include C-terminal kinase domain 303-648 and raf-CAAX (Figure 4; column 6; column 16, lines 55-65; column 27, lines 5-29; column 31,lines 4-5). They teach expression of the full length Raf and its fragments in host cells (column 18). They further teach isolation of Raf proteins by immunoprecipitation using a Raf specific antibody (column 14, lines 24-49).

Przybyszewska et al. teach that transfection of human urothelial cells (HCV-29) with v-raf results in two-fold increase of said cells ability to stimulate angiogenesis *in vivo* (abstract, page 159, Table 1). They teach that "it could be expected that raf plays a critical role in the induction of angiogenesis" (page 160, last paragraph). The teachings of Przybyszewska et al. provide the motivation to make a pharmaceutical composition comprising a raf protein to be administered for stimulation of angiogenesis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce c-Raf protein (SEQ ID NO:2) or its fragments by the expression in a host cell and isolating them therefrom using a specific antibody as

taught by Freed et al. Said host cell can be construed as a pharmaceutical compositions comprising c-Raf protein. Further, a buffer solution comprising an isolated c-Raf protein or its fragments represents a pharmaceutical composition (specification, page 35). The motivation to produce a buffer solution, i.e. a pharmaceutical composition comprising a c-Raf protein is provided by Freed et al. who teach its importance in various pathological conditions (columns 1-2). The teachings of Przybyszewska et al. provide the motivation to make a pharmaceutical composition comprising a raf protein to be administered for stimulation of angiogenesis. It would have been obvious to use a human homologue of v-raf, a c-Raf protein or its known active fragments taught by Freed et al., in said pharmaceutical composition. It is customary to make a pharmaceutical composition comprising at least 0.1 weight percent of an active ingredient.

It would have been further obvious to one of ordinary skill in the art that said pharmaceutical composition must be contained in some packing material such as a vial, for example, rendering it an article of manufacture comprising a pharmaceutical composition comprising a Raf protein of SEQ ID NO:2 or its fragments and an identifying label optionally containing instructions for use.

Statement of intended use in a pharmaceutical composition claim does not distinguish it over the prior art product, i.e. a pharmaceutical composition comprising Raf protein is the same product independent on its intended use.

Claims 1, 3, 6, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kolch et al. alone or in view of Przybyszewska et al.

Kolch et al. teach the production of the full length and truncated versions of the human c-Raf-1 protein (page 1046). They suggest the use of said purified proteins the production of antisera, for example (page 1048, last paragraph).

The teachings of Przybyszewska et al. are outlined above.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce c-Raf protein or its fragments by the expression in a host cell and isolating them therefrom using affinity chromatography as taught by Kolch et al. The motivation is provided by Koch et al. who suggest the use of said purified proteins the production of antisera, for example, *supra*. The solution of a protein used for the production of antisera meets the definition of a pharmaceutical composition according to the specification (page 35).

The teachings of Przybyszewska et al. provide the motivation to make a pharmaceutical composition comprising a raf protein to be administered for stimulation of angiogenesis. It would have been obvious to use a human Raf protein or its known active fragments taught by Kolch et al. in said pharmaceutical composition. It is customary to make a pharmaceutical composition comprising at least 0.1 weight percent of an active ingredient.

It would have been further obvious to one of ordinary skill in the art that said pharmaceutical composition must be contained in some packing material such as a vial, for example, rendering it an article of manufacture comprising a pharmaceutical

composition comprising a Raf protein of SEQ ID NO:2 or its fragments and an identifying label optionally containing instructions for use.

Statement of intended use in a pharmaceutical composition claim does not distinguish it over the prior art product, i.e. a pharmaceutical composition comprising Raf protein is the same product independent on its intended use.

Response to Arguments

Applicant's arguments filed May 21, 2004 have been fully considered but they are not persuasive.

With regard to the 103(a) rejections Applicants argue that "The present claims are directed to articles of manufacture, not to pharmaceutical compositions, not to specific Raf compounds, not to methods" (page 4). Applicants continue "Freed *et al.* do not teach or suggest all of the limitations of the presently claimed articles of manufacture. In particular they do not teach or suggest at least about 0.1 % by weight of the specific active Raf proteins contained within packaging material that has a label affixed thereto. Nor do Freed *et al.* teach or suggest that the Raf proteins stimulate angiogenesis, which is the subject matter of the writing on the label. Accordingly, this reference, alone, cannot render claim 1 obvious, since it does not teach or suggest all of the limitations of the claim" (page 4). This is not persuasive because as a reference in a 103(a) rejection, it does not need to teach all the limitations of the claims but only to make them obvious. As explained above, the reference definitely suggests a pharmaceutical composition that can be just a buffer solution intended for a treatment.

With regard to the limitation "consisting essentially of at least about 0.1 weight percent", practically any composition meets this limitation because it is an open range concentration. Thus, claim 1 encompasses any concentration starting from 0.1 percent. Applicants argue that "information on the label impart specific functionality to the article of manufacture that was previously unknown to one of ordinary skill in the art. The printed matter would distinguish the claimed articles of manufacture from other articles containing such a composition, were such article to have been known in the art" (sentences bridging pages 4-5, emphasis added). Applicants continue "Applicants take exception to the Examiner's comments that *Miller* and *In re Gulack* are not applicable here. In *Miller*, prior to adding the printed matter onto the measuring cup, that cup had utility as a simple cup. The new printed matter on the cup conveyed a new utility not previously known to one of ordinary skill in the art. Similarly, *In re Gulack*, 217 USPQ 401, 403 (CCPA 1983) involved a band imprinted with a series of digits derived from a mathematical algorithm. The band could be a hat band, for example, having utility on its own " (page 5). Applicants conclude "Clearly, in the present claims, the printed matter conveys a new utility to an article of manufacture that was not know in the art" (paragraph bridging pages 5-6). The examiner disagrees with the notion that in the instant case "information on the label imparts specific functionality to the article of manufacture". In the instant case "information on the label" does not impart specific functionality to the article of manufacture because the printed matter is not functionally related to the pharmaceutical composition. Said label and information printed thereon do not change the pharmaceutical composition. In *Miller*, prior to adding the printed

matter onto the cup, that cup did not have utility as a measuring cup but only as a simple cup. A measuring cup has properties that render it different from a simple cup. A measuring cup can be used as a simple cup but a simple cup cannot be used as a measuring cup without the printed matter. In the instant case, the pharmaceutical composition is unchanged by the label. A label is not a part of said composition. The examiner considers the instant case to be similar to *In re Ngai*, 70 USPQ2d 1862 (CAFC 2004). In *In re Ngai* the printed matter included in the kit was compared with *In re Gulack.* The CAFC stated that: "the printed matter in no way depends on the kit, and the kit does not depend on the printed matter. All the printed matter does is teach a new use for an existing product. As the Gulack court pointed out"[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability". Applicants argue "Przybyszewska et al. is directed to angiogenesis induced by urothelial cells that have been transformed by v-Ras and v-Raf, not c-Raf or fragments of c-Raf. This reference does not teach or suggest that c-Raf or its fragments, as isolated materials, can stimulate angiogenesis. Neither this reference nor Freed et al. nor the combination thereof teaches or suggests that c-Raf or its fragments have utility in a pharmaceutical composition or in an article of manufacture containing such a composition". This is not persuasive because while Przybyszewska et al. do not teach that c-Raf or its fragments, as isolated materials, can stimulate angiogenesis it makes it obvious. This is because urothelial cells stimulate angiogenesis only when transfected with v-Raf, i.e. due to the v-Raf presence. It is reasonable to expect that a highly homologous c-Raf has the same effect as v-Raf.

Applicants assert that "Kolch et al. describe preparation of human c-Raf expression vectors and transfection of cells with those vectors. This reference does not teach or suggest that c-Raf, per se, has utility in a pharmaceutical composition, nor does the reference teach or suggest an article of manufacture containing a minimum of 0.1% of c-Raf or its fragments in packaging material having a label including specific written matter affixed thereto. This reference does not teach or suggest all of the limitations of the claims" (page 6). This is not persuasive because even cells transformed with c-Raf can be construed as a pharmaceutical composition comprising c-Raf because said cells can be used to stimulate angiogenesis in animals. Furthermore, a solution of c-Raf can be construed as a pharmaceutical composition according to the specification (page 35). A vial containing said solution is an article of manufacture. Said vial or any other container should be labeled to provide at least the identification of the content. However, the printed matter does not change said content.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

August 2, 2004